REMARKS

Specification

By the present amendment, Applicants have deleted the previous priority claim, as amended by the Preliminary Amendment filed October 29, 2001, to cancel their claim to the priorities of U.S. application no. 09/835,243 and U.S. application no. 09/417,671; and have inserted in its place, paragraph [0001.1]. Upon entry of the amendment, Applicants submit that the priority claim will recite that the instant application is a continuation-in-part of U.S. application no. 09/606,909, filed June 29, 2000.

Claims

After entry of this amendment, claims 119-142 will be pending in the application. Claims 65, 67-72, 74-77, 79-82, 85-88, 90-93, 96-99, 101-106, 108-109, and 111-142 have been canceled without prejudice. New claims 119-142 have been added for purposes of clarity. No new matter has been added. Support for new claims 119-142 can be found, for example, in the table set forth below.

Claim Recitation	Support
119 intradermal space hollow needle depth outlet with exposed height improved systemic absorption	claims 1, 24, and 46 as originally filed ¶¶ 11, 25, 26; abstract Abstract, claim 1 as originally filed ¶ 15 ¶ 45 ¶¶ 22, 42; claims 24, 25, 30 and 47 as originally filed
120 Bolus	¶ 21
121 Infusion	¶ 21
122 monoclonal antibody	¶ 50, *l.* 12
123 pegylated antibody	¶ 50, *l.* 13
124 insulin	¶ 50, *l.* 8
125 vaccine	¶ 50, *l.* 21

126 carrier or adjuvant	¶ 50, *l.* 22
127 nanoparticles	¶ 47
128 microneedles	¶¶ 11, 26, 38; claims 24 and 35 as originally filed
129 needle outlet	¶ 45
130 outlet formed by a bevel	¶ 45
131 outlet formed by an opening	¶ 45
132 intradermal space hollow needle outlet with exposed height higher maximum plasma concentration higher bioavailability	claims 1, 24, 46 as originally filed ¶¶ 11, 25, 26; abstract abstract, claim 1 as originally filed ¶ 45 ¶¶ 11, 12, 18, 27, 42, 46 ¶¶ 11, 12, 17, 27
133 microneedles, catheter needles and injection needles	¶ 38
134 single needle	¶ 38
135 multiple needles	¶ 38
136 pressure directly on the liquid	¶ 46
137 hormone	¶¶ 11, 13, 16, 48
138 insulin, PTH	¶¶ 48, 49
139 about 0.5 to about 1.7 mm	¶ 15, claim 31 as originally filed
140 about 0.3 to 2 mm	abstract, ¶ 15, claim 6 as originally filed
141 0 mm	¶45
142 spacing of multiple needles	¶46

Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 65, 67-72, 74-77, 79-82, 85-88, 90-93, 96, 99, 101-106, 108, 109, 111-116, and 118 have been rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,848,991 to Gross *et al.* ("Gross") in view of U.S. Patent No. 6,056,716 to D'Antonio *et al.* ("D'Antonio"); or in view of D'Antonio, and further in view of U.S. Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton"). The Examiner alleges that Gross discloses a method of delivering drugs intradermally. While conceding that Gross fails to describe delivery by bolus administration, the Examiner asserts that bolus administration would be obvious to one of ordinary skill. The Examiner concedes that Gross fails to disclose that intradermal delivery achieves improved systemic absorption as compared with subcutaneous delivery, but contends that D'Antonio teaches intradermal injection shows better absorption than subcutaneous injection. The rejection of the claims is in error and should be withdrawn for the reasons detailed below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143. Here, a finding of obviousness cannot be supported because the combination of references fail to teach or suggest all the claim limitations. Second, the suggestion or motivation to modify the teachings of Gross with D'Antonio is absent.

First, new claims 119-131 specify injecting the substance into the intradermal space through a hollow needle comprising a needle outlet at a depth of about 0.3 to 2.5 mm, wherein the outlet has an exposed height of 0 to about 1 mm. Similarly, new claims 132-142 specify a method using a hollow needle wherein the outlet has an exposed height of 0 to about 1 mm. The exposed height of the needle outlet is not described nor suggested by any of the cited references. The cited references also fail to teach or suggest whether the outlet is located within the intradermal compartment. Placement of the needle outlet within the skin significantly affects PK/PD parameters. For instance, although a needle may be placed at a desired depth within the intradermal space, a needle outlet with a large exposed height causes the substance to be deposited at a much shallower depth nearer to the skin surface. As a

result, the substance tends to effuse out of the skin due to backpressure exerted by the skin itself and to pressure from accumulating fluid from the injection or infusion. *See* ¶ 45, lines 5-11 of the instant specification.

Gross fails to teach or suggest the exposed height of the needle used in the device that is used to deliver liquid drug into a subject. While disclosing with particularity the outer needle diameter and the needle length projecting from the disclosed drug delivery device, Gross fails to disclose the exposed height of the needle outlet. Nor does Gross teach or suggest the significance of confining the exposed height of the needle outlet within the intradermal space in achieving clinically useful PK/PD and dose accuracy.

Ganderton is equally silent as to teaching an exposed height of a needle outlet that is used to administer a substance to the intradermal space of a mammal. To clarify, the device of Ganderton consists of a permeable pad studded with spikes designed to puncture the stratum corneum of the skin to improve skin permeability. Drug is applied on top of the pad and when the pad is applied to the skin, the spikes puncture the outer layer of the skin and the drug subsequently diffuses onto the punctured skin. The drug is not actually delivered through the spikes of the device. Thus, Ganderton fails to teach use of hollow needles, let alone the exposed height of the outlet of a hollow needle.

Moreover, D'Antonio fails to remedy the deficiencies of Gross and Ganderton, as it relates to the delivery of injecting materials through *needle-less*, jet injectors. Thus, D'Antonio also fails to teach or suggest the exposed height of the needle outlet that is useful in the instantly claimed methods. Moreover, delivery systems that eliminate needles entirely, and rely on alternative methods to breach the stratum corneum, do not reproducibly breach the skin barriers or deliver the pharmaceutical substance to a given depth below the surface of the skin. Consequently, clinical results can be variable. *See* ¶ 2, lines 11-19.

Accordingly, for the reasons set forth above, Applicants respectfully submit that a finding of obviousness cannot be supported because the combination of references fail to teach or suggest all of the claim limitations.

Second, Applicants respectfully submit the rejection is improper because a suggestion or motivation to combine the teachings of Gross with D'Antonio is absent. Gross relates to the administration of liquid *drug*, and not to *vaccine* administration. On the other hand, the portion of D'Antonio that the Examiner apparently relies on to assert that the intradermal testing shows a better absorption than subcutaneous injection (*see* col. 29, lines 3-26) relates

to *vaccine* delivery, and not to *drug* delivery. D'Antonio describes the benefit of intradermal delivery in the context of *vaccine delivery* and the rapid and effective pick-up by the *immune* system. (D'Antonio, col. 29, *ll.* 23-26). One of skill in the art looking to administer a *drug* would not want rapid and effective pick-up by the immune system. Further, an immune response to a drug would be an adverse event which may require administration of more drug to achieve a therapeutic effect. Accordingly, such a prediction would likely lead one of ordinary skill to believe that an improved systemic absorption of drug would *not* result, based on the teachings of Gross and D'Antonio.

Moreover, Ganderton fails to remedy this deficiency since it relates to a device having a permeable pad with spikes designed to puncture the stratum corneum of the skin to improve skin permeability. It fails to teach or suggest a method comprising administering a substance into the intradermal space of a mammal, let alone that improved systemic absorption is produced upon administering the substance subcutaneously. At best, Ganderton suggests transdermal administration of a substance.

Accordingly, the combination of Gross with either D'Antonio, or with D'Antonio and Ganderton fails to suggest to one of ordinary skill that intradermal injection of a substance achieves improved systemic absorption relative to absorption produced upon administering the substance subcutaneously.

For the above mentioned reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully request that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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Respectfully submitted,

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